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Derivation and validation of a prediction model for risk stratification of post-thrombotic syndrome in patients with deep vein thrombosis

Running head: Derivation and validation of the post-thrombotic syndrome risk score

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ESSENTIALS

- Not all patients carry the same risk of developing a post-thrombotic syndrome
- Prediction models could estimate the risk of post thrombotic syndrome after a deep vein thrombosis
- Our prediction model is based on six predictors
- Patients at high risk of developing post thrombotic syndrome are accurately identified

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ABSTRACT

Background:

Not all patients carry the same risk of developing a post-thrombotic syndrome (PTS) after a deep vein thrombosis (DVT). We sought to derive a clinical prediction model to estimate the risk of PTS within 24 months of a DVT.

Methods:

Our derivation sample included 276 patients with a first acute symptomatic lower limb DVT enrolled in a prospective cohort. We derived our prediction rule using regression analysis, with the occurrence of PTS within 24 months of a DVT based on the Villalta score as outcome, and 12 candidate variables as predictors. We used bootstrapping methods for internal validation.

Results:

Overall, 161 patients (58.3%) developed a PTS within 24 months of a DVT. Our prediction rule was based on 6 predictors (age ≥75 years, lower extremity artery disease, prior varicose vein surgery, multilevel thrombosis, concomitant antiplatelet/NSAID therapy, and the number of leg symptoms and signs). Overall, 16.3%, 30.8%, and 52.9% of patients were classified as low (score 0-3), moderate (score 4-5), and high-risk (score ≥6), for developing a PTS. Within 24 months of the index DVT, 24.4% of the patients in the low-risk category developed a PTS, 38.8% in the moderate, and 80.1% in the high-risk category. The prediction model showed good discriminatory power (AUC 0.79; 95% confidence interval 0.74-0.84). Internal validation showed similar results.

Conclusions:

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This easy to use clinical prediction rule accurately identifies patients with DVT who are at high risk of developing PTS within 24 months who could potentially benefit from special educational or therapeutic measures to limit the risk of PTS.

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INTRODUCTION

Deep vein thrombosis (DVT) is a very common disease, with an annual incidence of 95 cases per 100,000 population [1]. The post-thrombotic syndrome (PTS), defined as chronic venous symptoms and/or signs secondary to DVT, is the most common long-term complication of DVT and occurs in 20% to 50% of patients within 2 years [2]. Patients with PTS often suffer from pain, heaviness, swelling, and cramping in the limb. These symptoms are aggravated by standing or walking and tend to improve with rest and recumbence [3, 4]. About 2 to 30% of patients with symptomatic DVT develop severe PTS that is characterized by the presence of painful venous ulcers [2]. Therefore, PTS has a measurable adverse impact on morbidity and quality of life [5-7]. The socioeconomic impact of PTS is significant with an estimated annual direct cost of US $200 million[8] and an annual loss of 2 million work days in the U.S [9]. Because existing treatment options for PTS are limited, prevention is a key measure to reduce the impact of this illness on morbidity, quality of life, and costs of care.

Growing evidence suggests that not all patients carry the same risk of developing PTS [10]. Several clinical factors apparent at time of DVT diagnosis, such as extensive proximal DVT, previous ipsilateral DVT, older age, body mass index >25 kg/m^2, vein insufficiency, inflammation and fibrinolysis, and residual vein obstruction appear to increase the risk of PTS [11-14]. D-dimer levels and suboptimal quality of anticoagulant therapy are other risk factors for PTS development [15-17]. To date, good anticoagulation quality is the only evidence-based modifiable risk factor for PTS prevention [13, 14, 18].

At present, no method accurately estimating individual risk for PTS development following a DVT is available. Therefore, an easy-to-use clinical

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prognostic model that accurately risk-stratifies patients with DVT would be very useful for medical decision-making. Patients at high-risk of developing PTS could benefit from special educational measures to achieve optimal quality of oral anticoagulant therapy, thus reducing the morbidity and costs related to this complication. Such patients could also be included in interventional research protocols designed to test whether prolonged anticoagulation course or treatment with direct oral anticoagulants could lower the incidence of PTS, or alternatively, whether they may benefit from early venous recanalization or elastic stocking compression. Our study objective was to derive a clinical prediction model for prognosis to estimate the risk of PTS within 24 months of an index DVT.

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METHODS

Study design, setting and participants

We used data prospectively collected from the SWIss venous Thromboembolism COhort (SWITCO65+) to develop our score. SWITCO65+ is a prospective multicenter cohort study that enrolled and followed up 1003 in- and outpatients aged ≥65 years with acute symptomatic, objectively confirmed deep vein thrombosis (DVT) and/or pulmonary embolism (PE) from all five university and four high-volume non-university hospitals in Switzerland between September 2009 and December 2013. Exclusion criteria were inability to provide informed consent (i.e., severe dementia), conditions incompatible with follow-up (i.e., terminal illness), insufficient German or French-speaking ability, thrombosis at a different site than lower limb, catheter-related thrombosis, or previous enrolment in the cohort. A detailed description of the study methods has been published previously [19]. The study was approved by the Institutional Review Board at each participating center. Because our aim was to derive a clinical score identifying patients at high-risk of PTS within 2 years after DVT, our analysis was restricted to patients with a first lower limb DVT episode to avoid the inclusion of patients with pre-existing PTS. The development of the prediction rule was guided by internationally recognized methodological standards [20-26].

Selection of predictor variables

In a first step, we identified clinical risk factors associated with the occurrence of PTS following an episode of acute symptomatic DVT, from the literature and we searched for these variables in the SWITCO65+ database [10, 12-14, 27]. To increase clinical applicability and acceptability of the score, we favored explicit and

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clinically plausible predictor variables that are easily available in a medical office setting. We did not consider potential predictors that are not routinely available (biomarkers of inflammation and fibrinolysis, or thrombophilic risk factors) [13, 14, 27]. We chose prior varicose vein surgery instead of primary vein insufficiency because the latter needs a confirmation by duplex ultrasound and was not available in the Switco65+ database. We did not consider potential predictors of PTS that were not available in the Switco65+ database (smoking during pregnancy, asymptomatic DVT, ipsilateral DVT recurrence) [14]. Since patients with iliofemoral DVT are a subset of patients with proximal DVT, and thus highly correlated to PTS, this variable was omitted from the model. Because our goal was to develop a score with a large applicability, we also considered common comorbid conditions, i.e. cancer related-VTE and lower extremity artery disease (LEAD), the latter sharing some clinical signs and symptoms with PTS. Symptomatic LEAD affects about 6% of patients aged >65 [28, 29]. The incomplete resolution of leg symptoms and signs one month after DVT was previously shown to predict PTS risk.[10] As this variable was not available in the SWITCO65+ database, we included leg symptoms and signs assessed at baseline as a proxy variable in the model.

Our final selection of candidate variables comprised 12 baseline predictors: age (≥75 years), gender (female), type of DVT (provoked versus unprovoked VTE, or cancer-related VTE), extent of thrombosis burden (concomitant PE, multilevel thrombosis, proximal DVT), increased body mass index (≥30 kg/m^2), prior varicose vein surgery, concomitant antiplatelet or NSAID therapy, LEAD and the magnitude of leg signs and symptoms at baseline [10, 12-14, 27].

Trained study nurses who prospectively collected baseline demographic information, comorbid conditions (such as LEAD, prior varicose vein surgery and

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concomitant antiplatelet or NSAID therapy) and DVT-related treatment using patient interviews and hospital chart review, obtained all baseline clinical variables used to derive our prediction rule. At the time of index DVT, study nurses also assessed the presence of DVT-related signs and symptoms (pain, cramps, heaviness, pruritus, paresthesia, edema, skin induration, hyperpigmentation, venous ectasia, redness, pain during calf compression) using standardized forms. Of note, duration of anticoagulant treatment, as well as elastic compression stockings, were prescribed at the treating physician's discretion.

Study outcome

The study outcome used to derive our prediction model was the occurrence of PTS within 24 months from index event based on the Villalta score.[30] The Villalta score is a clinical tool used to diagnose and categorize the severity of PTS. Five patient-rated symptoms (pain, cramps, heaviness, pruritus, and paresthesia) and six clinician-rated clinical signs (edema, redness, skin induration, hyperpigmentation, venous ectasia, and pain on calf compression) are graded depending on their presence and degree of severity from 0 points (absent) to 3 points (severe). Presence of PTS was defined as a Villalta score of ≥5 [31]. PTS severity is categorized as: mild (5 to 9 score points), moderate (10 to 14 score points), and severe (>14 score points or presence of a venous ulcer). The Villalta score is well validated, has good to excellent inter-observer reliability, and is responsive to clinical change [32, 33].

Patient follow-up included one telephone interview and two face-to-face evaluations during the first year of study participation, then semi-annual contacts, alternating between face-to-face evaluations (clinic visits or home visits in house-

bound patients) and telephone calls, as well as periodic reviews of the patient's hospital chart. Study nurses performed a standardized assessment of the PTS at 3, 12, and 24 months using the Villalta scale. Managing physicians were blinded to the Villalta results. Study nurses collected INR values obtained during the anticoagulation period.

During follow-up, trained vascular specialists assessed residual vein thrombosis within three months of the first DVT event. Residual vein thrombosis was defined as presence, in at least one affected vein, of a residual thrombus with a surface greater than 40% of diameter of the vein [34].

Statistical analyses

Derivation of the prediction model

The initial cohort comprised 1003 consenting patients with VTE. We excluded 557 patients with PE only, 109 with a history of prior DVT, and 16 with venous ulcer at baseline, leaving 321 patients with a first DVT. After the exclusion of another 45 patients (38 without PTS assessment during follow-up, 4 denying use of data, and 7 early consent withdrawals), our final study sample comprised 276 patients with a first acute DVT. We compared baseline characteristics of patients with and without PTS within 24 months using the chi-square test for categorical variables and the non-parametric Wilcoxon rank sum test for continuous variables. We assessed associations between preselected risk factors and PTS within 24 months as outcome variable using logistic regression.

We used backward selection to identify risk factors, removing variables with a p-value of >0.2. We evaluated model calibration, i.e. how accurately the model-based expected number of events matches the observed number of PTS in each risk

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group, using the Gronnesby and Borgan goodness-of-fit test for survival data.[35] We assigned one score point to each binary variable and each item of the continuous variable that were retained in the model and assessed the discrimination of the summed score, i.e. its ability to discriminate between patients who develop a PTS and those who do not, using the area under the receiver operating characteristic (ROC) curve. Additionally, we assessed the calibration of the score using the Brier score. We then classified patients into three categories of increasing risk (low, moderate, high) and calculated the observed risk of PTS at 3, 12, and 24 months for each risk category. We chose a cut-off point to identify patients who are at high- vs. lower risk of PTS at 24 months. While there is no universally accepted cut-off point for defining a high risk of PTS, we considered a 80% probability of developing a PTS as high and a 20% probability as low. Finally, we assessed the predictive accuracy for the high risk category (high versus moderate and low risk) calculating the sensitivity, specificity, and the positive and negative predictive value. Because the Villalta scale also classifies patients with PTS into severity categories, we assessed how good the score identifies severe PTS (Villalta score >14).

Internal validation of the prediction model

We used bootstrapping methods to assess the internal validity of the derived risk score. All steps from prediction modeling to score derivation were performed in each bootstrap cycle. Bootstrap sampling was performed 1000 times from the original sample, sampling the same number of patients as in the original sample with replacement. In each bootstrap sample, we derived a prediction model. Based on this model, the risk score was generated in the respective bootstrap sample as well as in the original sample. Performance measures, such as the AUC and the Brier

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score, were calculated from both samples. The difference in the performance measure between the two samples was subtracted from the original measure, yielding a bootstrap-corrected performance measure [36]. The 95% confidence intervals (CI) for the bootstrapped area under the ROC curve were derived using the percentile method. Additionally, we evaluated how often variables were selected in the bootstrap samples. All analyses were done using Stata 14 (Stata Corporation, College Station, Texas).

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RESULTS

Patient characteristics

Analyzed patients had a median age of 74 years, 46% were women, 32% had concomitant PE, and 18% presented an isolated distal DVT as the initial VTE event. The majority (60%) of DVT events was unprovoked and 17% of DVTs were cancer-related. Analyzed patients were similar to those excluded because of prior DVT in terms of age, gender, and comorbid conditions.

Overall, 161 patients (58.3%) developed a PTS within 24 months based on the Villalta score. Patients who developed a PTS were older and sicker than those without PTS (**Table 1**). Elastic compression stockings were prescribed in three quarter of patients after the acute DVT episode; however, the proportion of patients with PTS within 24 months did not vary according to compression stockings prescription (**Table 1**). Among patients with proximal DVT and an assessable leg vein ultrasonography performed at three months, 61% (n=171) had residual vein thrombosis. Residual vein thrombosis was more frequent in patients who developed a PTS at 24 months compared to those who did not, but this difference was not statistically significant (64% versus 54%, P=0.223). The median duration of initial anticoagulation was 6.3 months (interquartile range [IQR]: 3.3-19.7). Overall, patients spent 66.6% of time within the therapeutic range (IQR: 48.0-81.1) and 16.2 % of time (IQR 5.6-34.6) below the therapeutic range. The percentage of time within the therapeutic range did not vary significantly in patients with PTS compared to those without (65.3% versus 69.0%; p=0.123).

Derivation of the Prediction model

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Patient factors retained in the model after backward selection were age ≥75 years, presence of LEAD, prior varicose vein surgery, multilevel thrombosis, concomitant antiplatelet or NSAID therapy, and number of leg symptoms and signs. The latter included pain, cramps, heaviness, pruritus, paresthesia, edema, skin induration, hyperpigmentation, venous ectasia, redness, and pain during calf compression. Number of leg symptoms and signs was used as a continuous variable in the model to ensure a ratio of predictors to outcomes of around 1:10 to avoid model overfitting. Patients with PTS had a higher prevalence of these leg symptoms and signs than patients without PTS (**Table 1**). The scoring system shown in **Table 2** was used to assign points to each patient. Model calibration by the goodness-of-fit test showed a p-value of 0.12.

Overall, 16.3%, 30.8%, and 52.9% of patients were classified as low (score 0-3), moderate (score 4-5), and high-risk for PTS (score ≥6), respectively. Within 24 months of an index lower limb acute symptomatic proximal DVT, 24.4% of patients in the low-risk category developed a PTS, 38.8% in the moderate, and 80.1% in the high-risk category.

The selected model had a good discriminatory power for PTS within 24 months (AUC 0.79; 95% confidence interval [CI] 0.74-0.84), as well as for severe PTS (Villalta >14) within 24 months (AUC 0.82; 95% CI 0.67-0.96). Using a cut-off of ≥6 points to identify patients at high vs. lower risk of PTS at 24 months, sensitivity, specificity, and positive and negative predictive value of the score was 72.7%, 74.8%, 80.1% and 66.2% respectively (**Table 3**). The resulting score discriminated well between patients with and without PTS after 3, 12, and 24 months (**Table 4**).

Internal validation of the prediction rule

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In the bootstrap validation, the area under the ROC curve of the score was only slightly lower than that in the derivation cohort after 24 months (0.77; 95% CI 0.72-0.83, **Table 4**), indicating only little overfitting in the original prediction model. The variables most often selected in the bootstrap samples (>50%) were the same as the 6 predictors initially selected in the derivation cohort.

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DISCUSSION

Using high-quality data from a prospective cohort study, we derived an easy-to-use clinical score to predict the risk of developing a PTS within 24 months after an acute symptomatic proximal DVT. Six clinical predictors accurately identified patients at high risk of PTS. Internal validation confirmed the good discriminatory power of the score. To our knowledge, no other tool predicting the risk of PTS development after a first acute symptomatic proximal DVT exists to date.

To increase clinical applicability and acceptability of the score, we used only variables that are easily available in a medical office setting. Four predictors variables, i.e. older age, prior varicose vein surgery, multilevel thrombosis, and leg symptoms and signs are established predictors of PTS [11-13]. In our prediction model, concomitant NSAID or antiplatelet therapy at time of DVT was a predictor of PTS, which is in accordance with a previous study by Galanaud *et al* [27]. NSAIDs and antiplatelet therapy may be markers of comorbidity, such as cardiovascular or chronic orthopedic diseases, which both may present with leg symptoms mimicking PTS. One variable of the PTS, LEAD, was not previously identified as a predictor of PTS. Some of the symptoms of LEAD, such as cramps/pain, or skin changes may also be captured by the Villalta score and thus may generate a spurious association between LEAD and PTS.

The rule has important clinical and research implications. Given that no treatment for PTS exists, prevention remains a key measure. Evidence suggests that good anticoagulation quality effectively prevents PTS [14, 18]. In a prospective study, patients with a first DVT who spent more than 50% of their time below an INR level of 2.0 were almost three times more likely to develop a PTS [18]. Another recent multinational multicenter study confirmed this finding in 349 patients followed

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during six months after a first unprovoked DVT. During the first 3 months of therapy, the odds ratio for developing PTS if a patient had subtherapeutic anticoagulation during more than 20% of time was 1.84 (95% CI 1.13-3.01).[17]

Currently, European and American guidelines recommend providing anticoagulation of appropriate intensity and duration for treatment of initial DVT to decrease the risk of recurrent DVT and consequent PTS [14, 37]. The association between subtherapeutic anticoagulation with vitamin K antagonist (VKA) and subsequent PTS should encourage physicians to perform frequent and regular INR monitoring of patients receiving vitamin K antagonists, especially in the first months of treatment [14]. The net benefit of strategies aiming at improving the quality of long-term anticoagulation in patients at high risk of PT development might not only lower the PTS incidence but also have the potential to improve the quality of life after a first DVT event [5].

A recent large multicenter, placebo-controlled trial, enrolling 809 patients after a first episode of symptomatic proximal DVT assessed the effect of elastic compression stockings in preventing PTS [38]. In this trial, the use of compression stocking did not reduce PTS. Based on this recent evidence, guidelines suggest not to routinely use compression stockings to prevent PTS in patients with acute DVT.[14, 39] Because the application of elastic compression stockings remains reasonable to reduce symptomatic swelling in patients after a DVT, [37] physicians could restrict the prescription of elastic compression stockings to patients with a high risk of PTS according to the rule.

Finally, whether potential treatments, such as the use of direct oral anticoagulants, catheter-directed thrombolysis [14, 39], immediate mobilization after

DVT [40], exercise after DVT [41] and weight reduction [27] could reduce the risk of PTS in high-risk patients based on the score should be prospectively evaluated.

Limitations

The score has potential limitations. First, it was derived in patients aged 65 or older, which may limit the generalizability of its use. However, 55% of VTE occurs in patients older than 65 years old [42]. Moreover, our derivation cohort included a broad population of in and out patients with provoked and unprovoked DVT from university and non-university hospitals in Switzerland, thus increasing generalizability of the score [22]. Second, because direct oral anticoagulants were not authorized for treatment of acute DVT in Switzerland during the patient enrollment period, our score was developed in a sample of patients treated with VKA. Whether the score accurately predicts the risk of PTS in patients treated with direct oral anticoagulants, must be further studied.

In conclusion, we successfully derived and internally validated a practical score that accurately classifies patients with a first acute symptomatic DVT into three categories of increasing PTS risk. High-risk patients based on the score have an 80.1% probability to develop PTS and may be candidates for educational and therapeutic strategies aiming at decreasing the risk of developing PTS. Further validation of the score is mandatory before its implementation into clinical practice.

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AUTHOR'S CONTRIBUTION

MM conducted the study and wrote most of the article; AL made the statistical analyses and wrote part of the article; DA, AL, and AA, LM revised the article for important intellectual content: AL and MM had full access to the data and is the guarantor of the study. All authors have read and approved this version of the article.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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Table 1. Baseline characteristics by incidence of post-thrombotic syndrome within 24 months

	All	PTS within 24 months	No PTS within 24 months	
	n (%) or median (IQ-range)			p value
Total N	N = 276	N = 161	N = 115	
Patient age	74.0 (68.3; 80.0)	75.0 (70.0; 80.5)	71.0 (68.0; 77.0)	0.001
Age ≥75	128 (46)	88 (55)	40 (35)	0.001
Gender (female)	128 (46)	76 (47)	52 (45)	0.744
Type/severity of DVT				
Provoked DVT†	86 (31)	48 (30)	38 (33)	0.568
Concomitant PE	88 (32)	43 (27)	45 (39)	0.029
Proximal DVT	205 (74)	128 (80)	77 (67)	0.019
Distal DVT only	49 (18)	26 (16)	23 (20)	0.409
Highest extent				0.328
inferior vena cava	6 (2)	4 (2)	2 (2)	0.828
iliac vein	39 (14)	30 (19)	9 (8)	0.038
common femoral vein	46 (17)	27 (17)	19 (17)	0.552
superficial femoral vein	63 (23)	36 (22)	27 (23)	0.297
popliteal vein	51 (18)	31 (19)	20 (17)	0.778
Iliofemoral DVT‡	151 (55)	95 (59)	56 (49)	0.090
Multilevel thrombosis§	179 (65)	112 (70)	67 (58)	0.052
Comorbid condition				
LEAD	22 (8)	18 (11)	4 (3)	0.020
BMI >30	57 (21)	40 (25)	17 (15)	0.042
Prior varicose vein surgery	33 (12)	27 (17)	6 (5)	0.004
DVT-related treatment				
Concomittant antiplatelet/NSAID therapy	93 (34)	63 (39)	30 (26)	0.024
Prescription of compression stockings	201 (73)	117 (73)	84 (73)	0.945
Initial VKA therapy	240 (87)	143 (89)	97 (84)	0.277
Type of initial parenteral AC				0.600
LMWH	131 (47)	82 (51)	49 (43)	0.172
UFH	81 (29)	44 (27)	37 (32)	0.384
Fondaparinux	51 (18)	28 (17)	23 (20)	0.582
None	13 (5)	7 (4)	6 (5)	0.737
DVT signs/symptoms at baseline				
Pain	148 (54)	92 (57)	56 (49)	0.165
Cramps	96 (35)	67 (42)	29 (25)	0.005
Heaviness	105 (38)	75 (47)	30 (26)	0.001
Pruritus	49 (18)	37 (23)	12 (10)	0.007
Paresthesia	65 (24)	46 (29)	19 (17)	0.020
Edema	180 (65)	119 (74)	61 (53)	<0.001
Skin induration	62 (22)	51 (32)	11 (10)	<0.001
Hyperpigmentation	89 (32)	62 (39)	27 (23)	0.008

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Table 1 (continued)

	All	PTS within 24 months	No PTS within 24 months	
	n (%) or median (IQ-range)			p value
Venous ectasia	171 (62)	122 (76)	49 (43)	<0.001
Redness	99 (36)	69 (43)	30 (26)	0.004
Pain during calf compression	122 (44)	81 (50)	41 (36)	0.016
Number of leg signs and symptoms	4.0 (3.0; 6.0)	5.0 (4.0; 6.0)	3.0 (2.0; 5.0)	<0.001

Abbreviation: PTS: post-thrombotic syndrome ; IQ : interquartile ; DVT: deep vein thrombosis; BMI : body mass index ; NSAID : non steroidal anti-inflammatory drug; VKA: vitamin K antagonist, LEAD: lower extremity arterial disease

*Provoked index DVT: Transient risk factor (immobilization, major surgery or current estrogen therapy in the last 3 months).
†Proximal DVT with or without concomitant PE
§Distal DVT only (no concomitant proximal DVT nor PE)
‡Iliofemoral DVT: Thrombosis in iliac vein, and/or common femoral vein and/or superficial femoral vein.
**Multilevel thrombosis: Thrombosis in at least two veins.
††Active cancer: Solid or hematologic cancer requiring chemotherapy, radiotherapy, surgery, and/or palliative care during the last 3 months.

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Table 2: Post-thrombotic syndrome risk at 24 months in patients with proximal deep vein thrombosis

Post-thrombotic syndrome risk score			
Predictors	**OR (95% CI)**	**β-Coefficient (95% CI)**	**Points assigned**
Age ≥75 years	1.61 (0.91 to 2.86)	0.48 (-0.10-1.05)	+1
Concomitant antiplatelet/NSAID therapy	1.98 (1.05 to 3.71)	0.68 (0.05-1.31)	+1
Multilevel thrombosis	1.66 (0.93 to 2.98)	0.51 (-0.07-1.09)	+1
LEAD	2.50 (0.73 to 8.60)	0.91 (-0.32-2.15)	+1
Prior varicose vein surgery	2.82 (1.04 to 7.65)	1.04 (0.04-2.03)	+1
Number of leg signs and symptoms*	1.65 (1.40 to 1.95)	0.50 (0.34-0.67)	+1 (for each)
		AUC (95%CI)	
Model		0.79 (0.74-0.85)	

Abbreviations: OR: odds ratio; CI : confidence interval ; NSAID : non steroidal anti-inflammatory drug, LEAD: lower extremity arterial disease ; AUC : area under the ROC curve.

* pain, cramps, heaviness, pruritus, paresthesia, edema, skin induration, hyperpigmentation, venous ectasia, redness, pain during calf compression.

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Table 3: Predictive accuracy for risk category ≥6 points (high versus medium/low risk)

PTS	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Within 3 months	76.9 (68.1 - 83.8)	62.5 (55.0 - 69.5)	56.8 (48.7 - 64.6)	80.8 (73.2 - 86.6)
Within 12 months	72.9 (65.0 - 79.5)	67.6 (59.4 - 74.9)	69.9 (62.0 - 76.7)	70.8 (62.4 - 77.9)
Within 24 months	72.7 (65.3 - 79.0)	74.8 (66.1 - 81.8)	80.1 (72.9 - 85.8)	66.2 (57.7 - 73.7)

Abbreviation: PTS : post-thrombotic syndrome ; PPV : positive predictive value ; NPV : negative predictive value ; CI : confidence interval

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Table 4: Performance of the post-thrombotic syndrome risk score prediction over time

Pronostic Model	**Derivation sample**		**Internal validation**	
PTS	AUC (95%-CI)	Brier score	AUC (95%-CI)	Brier score
Within 3 months	0.76 (0.71 to 0.82)	0.19	0.75 (0.70 to 0.81)	0.19
Within 12 months	0.75 (0.69 to 0.80)	0.20	0.73 (0.68 to 0.79)	0.21
Within 24 months	0.79 (0.74 to 0.84)	0.18	0.77 (0.72 to 0.83)	0.19

Abbreviation: PTS: post-thrombotic syndrome